REMARKS

Claims 101-125 are pending. Claims 101, 108-109, 111 and 113-114 are amended. The amendments are supported by the application as filed, thus there is no issue of new matter. Claims 103-107, 110 and 125 are cancelled without disclaimer or prejudice to applicants' right to pursue patent protection for the subject matter thereof in another application. Claims 101-102, 108-109 and 111-124 thus appear in the application for the Examiner's review and consideration.

Support for the claim amendments is found, *inter alia*, in the specification as follows: **Claim 101**: page 13, lines 8-10, page 14, lines 1-5 and page 53, line 35 to page 54, line 4; **Claims 108-109**: dependencies changed from claim 107 to 101 due to the cancellation of claim 107; **Claim 111**: page 13, lines 8-10; **Claim 113**: page 13, lines 8-10, page 14, lines 1-5 and page 53, line 35 to page 54, line 4; **Claim 114**: page 13, lines 8-10, page 14, lines 1-5, page 15, line 27 to page 16, line 5, page 53, line 35 to page 54, line 4, and the Experimental Results discussed at pages 36-118.

Applicants note their appreciation for the courtesies extended by Examiner Holleran and her Supervisor, Examiner Anthony Caputa, to their representatives John P. White, Esq. and Mark A. Farley, Esq. during a telephone interview concerning related application Serial No. 08/196,154 on Tuesday, December 2 2003. The amendments and comments submitted in this response are in accordance with the matters discussed during that telephone interview and thus constitute a written record thereof.

REJECTIONS WITHDRAWN

In ¶4 of the Office Action the Examiner stated that the provisional double-patenting rejection of claims 101-125 over Application No. 08/477,097 is withdrawn upon further consideration because the claims of the instant application are drawn to conjugates comprising

a GD3 ganglioside, whereas the claims of 08/477,097 are drawn to conjugates comprising either the GD2 or GM2 gangliosides.

In ¶5 of the Office Action the Examiner stated that the provisional double-patenting rejection of claims 101-125 over Application No. 08/196,154 is withdrawn upon further consideration because the claims of the instant application are drawn to conjugates comprising a GD3 ganglioside, whereas the claims of 08/196,154 are drawn to conjugates comprising the GM2 ganglioside. The Examiner stated that Applicants argue that the claims of 08/196,154 do not render obvious the instant claims and that Applicant's arguments filed 6/10/96 have been fully considered but they are not persuasive because Applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

In ¶6 of the Office Action the Examiner stated that the rejection of claim 95 [*sic. 96*] under 35 U.S.C. 103(a) over Wiegand et al. (U.S. Patent 5,599,914), in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology,146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 78, 80-92, 94 and 96-99 and further in view of Irie (U.S. Patent 4,557,931) is withdrawn upon further consideration of the teachings of Irie with respect to the expression of GD3 ganglioside expression in epithelial tissues.

OBJECTIONS/REJECTIONS MAINTAINED

The Examiner stated in ¶7 of the Office Action that the prior objection to the disclosure is maintained for the reasons set forth in the Office Action mailed 6/10/96 (Paper No. 9). The Examiner stated

that Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance, but until applicants submit a proper Figure the objection is maintained.

In Paper No. 9 the Examiner stated that on page 5, line 30 of the application, in the Brief Description of the Figures, Figure 6b is listed as graphing IgG antibodies but Figure 6b has the Y-axis labeled as IgM titer. The Examiner stated that the appropriate correction is required.

Attached hereto as **Exhibit A** is an annotated (marked-up) copy of Figure 6B indicating in red ink a proposed change wherein the Y-axis is now labeled as "IgG". **Exhibit B** is a replacement drawing sheet with the above-indicated change made to the labeling of the Y-axis. The amendment to Figure 6B is supported by page 5 of applicants' specification. Applicants respectfully request entry of this drawing correction as it raises no question of new matter. The Examiner is requested to reconsider and withdraw the objection to the disclosure in view of the submission of the corrected Figure.

Double-Patenting Rejection

In ¶8 of the Office Action the Examiner stated that the provisional rejection of claims 101-125 for obviousness-type double patenting over claims 123-146 of Application No. 08/477,147 is maintained for reasons made of record in Paper No. 23, mailed 10-5-99 and in paper No. 25, mailed 6-19-2000. The Examiner stated that applicants argue that the claims of 08/477,147 do not render obvious the instant claims. The Examiner stated that applicants' arguments filed 6/10/96 have been fully considered but they are not persuasive because applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

In response to this provisional rejection, submitted herewith as

Exhibit C is a Terminal Disclaimer over any patent issued from U.S. Serial No. 08/477,147. The disclaimer has been executed by an authorized representative of Sloan-Kettering Institute for Cancer Research, i.e., the Assignee of both the subject application and U.S. Serial No. 08/477,147. As set forth in §804 IB in the Manual of Patent Examining Procedure, the "provisional" double-patenting rejection will become an "actual" double-patenting rejection if U.S. Serial No. 08/477,147 issues as a patent either prior to or on the same date as the subject application. The effect of the terminal disclaimer would be to prevent the term of any patent based on the subject application from extending beyond the term of the patent based on U.S. Serial No. 08/477,147. The Examiner is respectfully requested to reconsider and withdraw the provisional double-patenting rejection of claims 101-125.

Rejections Under 35 U.S.C. §103(a)

In ¶9 of the Office Action claims 101-111 are rejected under 35 U.S.C. 103(a) over the combination of six references, i.e., Wiegand et al (U.S. Patent 5,599,914) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437,1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

In ¶10 claims 101, 111-114 and 116-125 are rejected under 35 U.S.C. 103(a) over the combined disclosure of eight references, i.e., Wiegand et al (U.S. Patent 5,599,914), Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

In ¶11 claims 114 and 115 are rejected under 35 U.S.C. 103(a) over the eight references discussed in the paragraph above in combination with a 9th reference which is newly cited in the present Office Action, namely Diatlovitskaia et al. (Biokhimiia, 56(3): 560-564, 1991, Mar.; Abstract only). The Examiner stated that Diatlovitskaia teaches that the ganglioside GD3 is expressed in breast carcinoma, which is an example of a cancer of epithelial origin.

It is respectfully noted that the first eight references relied upon, in combination, to reject the claims under 35 U.S.C. §103(a) have been discussed in detail in, *inter alia*, applicants' Amendment In Response To August 27, 2002 Office Action filed March 17, 2003 wherein applicants described several features which they submit distinguish the invention. These arguments are incorporated by reference herein and thus are not repeated here. Applicants have now, moreover, amended the claims such that, as discussed below they now recite several additional features which patentably distinguish the invention over the prior art.

The Inclusion Of The Adjuvant QS-21 Provides Unexpected Results That Demonstrate The Non-Obviousness Of The Invention

Composition claims 102, 108, 109 and 111 and method claim 112 recite that the composition of the invention includes the adjuvant QS-21, i.e., a saponin derivable from the bark of a Quillaja saponaria Molina tree. Moreover, claims such as 101 and 113-114 recite the presence of a saponin derivable from the bark of a Quillaja saponaria Molina tree which, by definition, encompasses the adjuvant QS-21. During the December 2nd telephone interview the attention of the Examiner and her supervisor was directed to pages 94-95 of the present specification, which describe unexpected results achieved with the compositions of the invention using QS-21 as an adjuvant, in comparison to the results obtained with the use of prior art

adjuvants, i.e., BCG and DETOX.

Briefly, the specification teaches that local reactions to dosages of 100-200 µg of QS-21 were "quite different" (p.94, line 5) than those seen with comparable dosages of the prior art adjuvants BCG and DETOX. It further states that the local response is more diffuse than the response generally seen with doses of DETOX or BCG inducing comparable systemic symptoms (lines 8-11). It additionally teaches (lines 11-16) that a surprising feature of the subjects' response to QS-21 was that several days later (at most 10 days later) the local reactions had completely abated and there was no evidence that the vaccination had been administered to that site.

Applicants' specification additionally teaches (see paragraph bridging pps. 94-95) that QS-21, at any of the dosages used, resulted in a qualitatively different response than those achieved with the prior art adjuvants to GM2 ganglioside. The results obtained with QS-21 were contrasted with the immunogenic response achieved with the use of GM2-KLH vaccines alone or with optimal doses of BCG or DETOX, which were demonstrated to be substantially less effective than comparable compositions including QS-21. The specification additionally teaches that the results achieved by applicants demonstrate that the 100 and 200 µg doses of QS-21 induce the optimal antibody response against GM2 and that the 100 µg dose is better tolerated. These dosages are recited in the claims.
To summarize, applicants contend that the inclusion of QS-21 in their claimed compositions produces two unexpected improvements over the results achieved with the prior art BCG and DETOX adjuvants: (1) the side effects attributed to such adjuvants are ameliorated with the use of QS-21 and (2) even at the lowest doses of the QS-21 adjuvant, all of patients tested produced IgG antibodies. Applicants' claims identified above specifically recite the presence of the QS-21 adjuvant in an amount of about 10 µg and about 200 µg

(i.e., by virtue of claim 102's dependency from claim 101). Applicants contend that these recitations patentably distinguish the invention from the prior art.

During the December 2 2003 interview the Examiner inquired whether the results attributable to the inclusion of QS-21 were truly unexpected in light of the disclosure of the Kensil et al. reference. Applicants' representative pointed out that the reference does not suggest the use of QS-21 as an adjuvant and, in fact, teaches away from such use. For instance, page 435 of Kensil et al. makes clear that QS-7 adjuvant is more advantageous than QS-21 in that QS-7 is both less toxic and less hemolytic than QS-21. These advantages of QS-7 over QS-21 are important since the adjuvant is to be combined with the conjugate (discussed below) for administration to human subjects to stimulate or enhance the production of antibodies and/or to treat a human subject having cancer. Clearly, the increased toxicity and hemolytic activity of QS-21 disclosed in Kensil teaches away from the use of QS-21 and toward the use of QS-7. In summary, Kensil et al. would not lead one of ordinary skill in this art to expect the surprising results achieved using QS-21 as the adjuvant, which results demonstrate the non-obviousness of applicants' claimed invention.

The Claimed Conjugate And The Molar Ratio Of Conjugated Ganglioside Derivative To Keyhole Limpet Hemocyanin Provide Additional Evidence Of Patentability

The claims recite, inter alia, (1) a conjugate of a GD3 lactone ganglioside derivative and Keyhole Limpet Hemocyanin, and (2) that the GD3 lactone:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1. As explained below, these features serve to further distinguish the invention from the prior art relied upon to reject the claims.

The primary reference cited by the Examiner is U.S. Patent No. 5,599,914 to Wiegand et al. ("Wiegand"). Wiegand discloses, e.g., at col. 7, lines 1-8, that the ganglioside derivatives (GM3, GD3, GM2 and GM1) were reacted with Human Serum Albumin, i.e., not Keyhole Limpet Hemocyanin as recited in applicants' claims, and that the HSA was derivatized with 16-18 SPDP molecules. The reference also teaches that this level was the preferred level (see, e.g., col. 7, lines 1-3). In contrast, applicants' claims recite a GD3 lactone:Keyhole Limpet Hemocyanin molar ratio of between 200:1 and 1400:1. Such a ratio is neither taught nor suggested by Wiegand. The subject reference teaches away from the present invention due to its teaching that the derivatization level of 16-18 is the "desired" level, and in view of the use of Human Serum Albumin as the protein carrier instead of Keyhole Limpet Hemocyanin as recited in applicants' claims. There is no disclosure in the reference, moreover, which would suggest the replacement of Human Serum Albumin with Keyhole Limpet Hemocyanin, or to produce a conjugate having a derivatization level different than that disclosed in Wiegand.

The Examiner combined Wiegand patent with Fiume et al. ("Fiume"), stating that, "Wiegand in combination with Fiume teaches a glycoconjugate as claimed in claim 78 [*sic*, claim 101]." Applicants respectfully traverse this contention for the reasons which follow. The portion of Fiume cited by the Examiner (commencing at page 268) states that a drawback to the clinical use of the conjugates disclosed by the reference is their immunogenicity. The thrust is therefore to find a methodology for reducing the immunological effect of these conjugates. This teaching is opposite to that provided by the applicants about their invention in that the purpose of the conjugates of the present invention, as well as the methods of using these conjugates, is to increase, not to reduce, the immunogenic effect of the conjugates (see, e.g., claim 113)

Fiume not only teaches away from the present invention, it contains no disclosure which would suggest its combination with Wiegand. Wiegand discloses the formation of a composition for use in producing an immunogenic response. In contrast, Fiume teaches to proceed in a diametrically opposed direction, i.e., to seek compounds having a reduced immunogenic effect. These contrasting teachings would lead a skilled artisan away from combining Wiegand and Fiume. Further, even if combined, such combination would not produce the claimed glycoconjugate.

The Improved Results Obtained With Applicants' Compositions Evidence The Patentability Of These Compositions

Applicants previously provided the Examiner with a reference by Chapman et al., Clinical Cancer Research, Vol. 6, pp. 874-879 (March 2000) entitled, "Induction of Antibodies Against GM2 Ganglioside By Immunizing Melanoma Patients Using GM2-Keyhole Limpet Hemocyanin + QS21 Vaccine: A Dose-Response Study" (hereinafter "Chapman"). For the Examiner's convenience, another copy of this reference is provided herewith as Exhibit D to this Amendment.

As noted, e.g., at pages 26-27 of the Amendment filed by applicants on April 12, 2002, in clinical trials melanoma patients vaccinated with GM2-KLH + QS-21 made using the conjugation procedure described in the present application, produced high titer IgM and IgG antibodies specific for GM2. These clinical results thus led the authors (including Dr. Philip O. Livingston, a co-inventor of the presently claimed invention) to state that the GM2-KLH/QS-21 composition, "is more immunogenic than our previous formulation." (see Abstract). The "previous formulation" comprised GM2 and bacilli Calmette-Guerin (BCG).

The Livingston paper and the Livingston '663 U.S. Patent both disclose the GM2-BCG formulation, i.e., the "previous formulation".

The improved formulations described in the present application and claimed herein are distinguishable over in that the "previous formulations" do not comprise the same components as the compositions now recited in applicants' claims. Further, not only are applicants' formulations made with different components, the present claims additionally recite specific ranges for the components included in these formulations. As demonstrated in Chapman, the presently claimed compositions produce significantly improved results in contrast to those achieved with the previous formulations.

In summary, therefore, the presently claimed compositions are distinguishable from those disclosed in the Livingston references as, due to (1) differences in the components from which they are formed and (2) the relative amounts of the conjugate and the saponin included in these present compositions (as recited in applicants' claims), they produce a substantially improved immune response (i.e., in comparison to that achieved with the use of the prior formulations) when administered to subjects in a clinical setting.

The remaining references cited by the Examiner, i.e., Ritter et al. and Uemura et al., which were cited by the Examiner in prior Office Actions, as well as the newly-cited Diatlovitskaia reference, do not contain any disclosure which would remedy the deficiencies of the references discussed above. Diatlovitskaia, as noted above, is cited simply due to its disclosure that the ganglioside GD3 is expressed by breast carcinomas, which is an example of a cancer of epithelial origin (see page 11, lines 5-6 of the Office Action) The disclosure of this newly-cited reference (or the two other above-mentioned references) thus fails to overcome the deficiencies of the references it is combined with as discussed above. Applicants submit that the invention as now recited in the claims is distinguishable from, and thus <u>not</u> obvious over, the prior art references cited to

reject applicants' claims and respectfully request that the Examiner reconsider and withdraw all of the rejections of the claims under 35 U.S.C. §103(a).

NEW GROUNDS OF REJECTION

In ¶13 on page 12 of the Office Action claims 104-106 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner stated that claims 104-106 recite ranges that are not described in the specification. Claims 104-106 are cancelled herein and thus the §112 rejection of these claims is moot.

The Examiner additionally stated that claim 125 is drawn to a method for delaying recurrence of melanoma. The Examiner stated that there does not appear to be support in the specification for methods for delaying recurrence of melanoma. The Examiner stated that the passages pointed to by applicants as providing support do not teach the recited references and do not teach methods for delaying the recurrence of melanoma. In response, claim 125 has been cancelled and thus the rejection of that claim is also moot.

SUMMARY

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection set forth in the Office Action and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' attorneys invite the Examiner to telephone either of them at the number provided below.

A check for FIVE HUNDRED AND THIRTY DOLLARS ($530.00) is enclosed herewith. This amount has been determined by adding the fee of $475.00 due under 37 C.F.R. §1.17(a)(3) for the three-month extension of time for filing this response to the fee of $55.00 due under 37 C.F.R. §1.20(d) for the filing of the Terminal Disclaimer ($475.00 + $55.00 = $530.00). If any additional fees are required, authorization is hereby given to charge the amount of such required fee(s) to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Arlington, VA 22313-1450.

Mark A Farley 12-10-03

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